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REVIEW ARTICLE

Cancer immunotherapy: the art of targeting the tumor immune microenvironment

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Abstract

For many decades, cancer treatment has been strongly directed toward the development of cytotoxic and cytostatic drugs, quite often leading to disappointing results due to the inter- and intra-tumoral heterogeneity. Lately, this intra-cellular look has given way to the understanding of the tumor microenvironment, thus enabling modification of the immunological dynamics between tumor cells and their host. An era of new drugs aiming to unlock the host immune system against tumor cells is steadily increasing. Strategies involving adoptive cell therapy, therapeutic vaccines, immune checkpoint inhibitors and so on have provided spectacular clinical responses and increased survival in previously refractory settings and "hard-to-treat" cancers. Based on a comprehensive search in the main scientific databases, annals of recent renowned oncology congresses and platforms of ongoing trials, the clinical pharmacology characteristics of the main classes of immunotherapeutic agents, as well as the new treatment strategies related to immunotherapy in solid tumors, are carefully discussed throughout this review.

Keywords Immunotherapy · Immune microenvironment · Adoptive cell therapy · Therapeutic vaccines · Immune checkpoints inhibitors

Abbreviations

NK	Natural killers cells
ACT	Adoptive cell transfer therapy
CR	Complete response
CARs	Chimeric antigen receptors
TCR	Linked to T cell receptor
MHC	Major histocompatibility complex
TILs	Tumor-infiltrating lymphocytes
SD	Stable disease
EBViNT	EBV-induced natural T cell
APCs	Antigen-presenting cells
FDA	Food and drugs administration
HR	Hazard ratio
DC	Dendritic cell
RR	Response rate
CTLA-4	T lymphocyte-associated antigen 4
PD-1/PD-L1	Programmed cell death protein 1 pathway
iRAEs	Immune-related adverse events
irRC	Immune-related response criteria
PD	Progressive disease
OS	Overall survival
ITT	Intetion-to-treat
PR	Partial response
MSI-H	Microsatellite instability-high
dMMR	Mismatch repair deficient
IDO	Indoleamine 2,3 dioxygenase

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Introduction

Initially, in 1909 some scientists suggested that the immune system could have some role in cancer response [1]. Thereafter, in 1957 other colleagues postulated a new theory about cancer immunosurveillance indicating that the immune system could have the ability to perceive the abnormal cells, destroying them and consequently preventing tumor growth [2]. Unlike former cancer therapies that directly target malignant cells, immunotherapeutic agents stimulate the body's immune system to target and

attack the tumor, which is otherwise invisible or resistant to the immune response. However, the definitive evidence that different types of immunotherapy can have therapeutic benefits in cancer treatment has been acquired only recently.

Cancer immunotherapy involves the use of a wide variety of therapeutic modalities such as cytokines, vaccines, cell therapies and transfection agents that stimulate the host's antitumor response by increasing the effector cells, as well as other agents that decrease the host's suppressor mechanisms by modifying tumor environment through the modulation of immune checkpoints. Therefore, immunotherapy comprises treatments that enhance the innate power of the immune system to combat cancer [3].

In other words, cancer immune treatment benefits the host by inhibiting tumor progression as well as shaping the microenvironment composition of the emerging tumor. Initially described by Schreiber et al. [4] as an "immunoediting" process, the interaction dynamics of host and tumor cells evolves sequentially through the phases of elimination, equilibrium and escape, resulting in deep modification of innate and adaptive immune responses throughout the tumorigenesis. Firstly, emerging transformed cells are inhibited by immune effector cells of the innate immune response, natural killer (NK) cells, and by the host effector molecules, such as IFN-γ perforin, Fas/FasL, and TRAIL. Secondly, this process leads to immune selection and immune sculpting that, subsequently, induce tumor variants with low immunogenicity and resistance to immune effector cells in the equilibrium phase. However, the molecular mechanisms that trigger this phase remain poorly understood. Lastly, tumors perform several strategies to avoid recognition by the immune system, enabling them to grow and spread undetectably. This phase of tumor cell escape can involve reduced immune recognition, increased resistance, cell survival and the release of soluble factors that foster an immunosuppressive tumor microenvironment [5].

Tumor development and progression are usually accompanied by a large burden of mutations and re-expression of embryonic genes leading to the translation into neoantigens that can be recognized by T cells [6]. Shankaran et al. [7] consistently reported the process of recognition and control of tumor growth by T cells. Through an experiment involving a comparative analysis of the behavior of carcinogen-induced tumors in immunodeficient and wild-type mice, the T cell reactivity was crucial for the immunogenicity of mature tumors. More recently, these definitions have been reaffirmed and recognized as a hallmark of cancer [8]. However, this mechanism is not always effective in the eradication of cancer cells during the tumor development. Low mutational rates or improper antigen presentation might result in unsatisfactory interactions between tumor antigen and specific T cells. Moreover, the tumor antigen-specific T cell pairs are not always capable of spreading homogenously through the tumor microenvironment [9].

Based on a favorable modification of the tumor microenvironment with promising clinical results, immunotherapy has become a critical tool for approaching cancer in several sites. Through a comprehensive search in the main scientific databases, annals of recent renowned oncology congresses and platforms of ongoing trials, the main objective of the current study is to carry out a broad and updated review of the main classes of immunotherapeutic agents used in cancer management as well as to discuss the new trends of translational research in progress in solid tumors. For further understanding, Table 1 summarizes the key studies addressed to the main classes of immunotherapeutic agents, while Table 2 outlines the year some new drugs have been approved by the Food and Drug Administration (FDA) and their respective indications for a wide variety of settings. Moreover, a diagram with an overview on the new challenges and future directions in this field is wisely presented in Fig. 1.

Adoptive cell therapy

Adoptive cell transfer therapy (ACT) functionally modifies T lymphocytes, leading them objectively to recognize and attack a broad spectrum of specific cell targets, setting it up as a powerful therapy in the context of advanced cancer. The main approaches to cell therapy involve autologous tumor-infiltrating lymphocytes (TILs) selected for their antitumor reactivity or autologous T cells genetically engineered with TCRs or chimeric antigen receptors (CARs), as well as the emerging natural killer cells engineered with CARs. As a promising therapeutic tool in development, some interesting but still conflicting results using ACT have been published in small reports for some types of solid tumors. And in this context, some challenges have been faced in the use of ACT in solid tumors, since they often present with primary sites with difficult infiltration of infused T cells, are composed of a microenvironment known as immunosuppressive and have heterogeneous expression of antigens [10].

Preliminary data have shown clinical benefit of ACT based on autologous tumor-infiltrating lymphocytes (TILs) for patients with advanced solid tumors as a highly personalized treatment. T cells are obtained from autologous fresh tumor tissues and, after ex vivo activation and extensive expansion, are reinfused to patients, enabling the successful trafficking of T cell to the tumor microenvironment [11]. Although some early phase I/II studies in a few specialized care centers have consistently shown significant responses, mainly in melanoma, performing complete durable regressions in over 20% of patients, the production of TILs remains very costly and complex [12]. As for non-melanoma tumors,

Table 1 Key studies with immunotherapy

Agents	Indication	Design/study	Regimen	Results	References
ACT	Melanoma	Phase II	TILs + chemotherapy	ORR 50%	[21]
Vaccines	Castration-resistant prostate cancer	Phase I	Sipuleucel-T vs placebo	OS 25.8 vs 21.7 months (HR 0.73; $p = 0.001$)	[27]
Immune checkpoints blockade					
Anti-CTLA-4	Melanoma	Phase III	Ipilimumab 3 mg/kg vs gp100	OS 10.1 vs 6.4 months (HR 0.68; $p < 0.001$)	[43]
	Melanoma	Phase III/EORTC 18071	Ipilimumab 10 mg/kg vs placebo	5 year RFS 40.8% vs 30.3% (HR 0.76; $p < 0.001$)	[44]
	Melanoma	Phase III	Tremelimumab 15 mg/kg vs chemotherapy	OS 12.6 vs 10.7 months (HR 0.88; $p < 0.127$)	[49]
Anti-PD1	Melanoma	CHECKMATE-238 (phase III)	Nivolumab vs ipilimumab	12 months rate RFS 70.5% vs 60.8% (HR 0.65; $p < 0.001$)	[53]
		KEYNOTE-006 (phase III)	Pembrolizumab vs ipilimumab	OS NR vs 16 months (HR 0.68; $p = 0.0009$)	[45]
	NSCLC	KEYNOTE-024 (phase III)	Pembrolizumab vs docetaxel	PFS 10.3 vs 6.0 months (HR 0.50; $p = 0.005$)	[96]
		KEYNOTE-021 (phase I/II)	Chemotherapy ± pembrolizumab	ORR 55% vs 29%	[62]
		KEYNOTE-189 (phase III)	Pembrolizumab ± chemotherapy	PFS 8.8 vs 4.9 months (HR 0.52; $p < 0.001$)	[63]
		KEYNOTE-042 (PD-L1 ≥ 1%; phase III)	Pembrolizumab vs chemotherapy	OS 16.7 vs 12.1 months (HR 0.81; $p = 0.0018$)	[97]
	Renal cell carcinoma	Phase III	Nivolumab vs everolimus	OS 25.0 vs 19.6 months (HR 0.73)	[54]
	Platino-refractory SCCHN	CHECKMATE-141 (phase III)	Nivolumab vs chemotherapy	OS 7.5 vs 5.1 months (HR0.7; $p = 0.01$)	[55]
		KEYNOTE-012 (phase Ib)	Single-arm pembrolizumab	ORR 16.0% (95% CI 11–22)	[98]
	Urothelial carcinoma	KEYNOTE-052 (phase II)	Single-arm pembrolizumab	ORR 29.0% (95% CI 24–34)	[66]
		CHECKMATE-275 (phase II)	Single-arm nivolumab	ORR 19,6% (95% CI 15.1–24.9; 53/270)	[56]
	Colorectal cancer	CHECKMATE-142 (phase II)	Single-arm nivolumab	ORR 28% (95% CI 20.8–42.9)	[57]
	HCC	CHECKMATE-040 (phase I/II)	Single-arm nivolumab	ORR 20% (95% CI 15–26).	[58]
	Cervical cancer	KEYNOTE-158 (phase II)	Single-arm pembrolizumab	ORR 14.3% (95% CI 7.4–24.1)	[67]
		KEYNOTE-028 (phase Ib)	Single-arm pembrolizumab	ORR 17.0% (95% CI 5–37)	[99]
	Gastric cancer	KEYNOTE-059 (phase II)	Single-arm pembrolizumab	13.3% (95% CI 8.2–20.0)	[68]
Anti-PDL1	NSCLC	OAK (phase III)	Atezolizumab vs docetaxel 75 mg/m^2	OS 13.8 vs 9.6 months (HR 0.73; $p < 0.001$)	[71]
		IMpower 150 (phase III)	Carboplatin/paclitaxel/bevacizumab ± atezolizumab	OS 19.2 vs 14.7 months (HR0.78; $p = 0.016$)	[72]
		PACIFIC (phase III)	Adjuvant chemoradiotherapy ± durvalumab	PFS 16.8 vs 5.6 months (HR 0.52; $p < 0.001$)	[84]
	Urothelial carcinoma	IMvigor211 (phase III)	Atezolizumab vs chemotherapy	OS 11.1 vs 10 months (HR 0.87; $p = 0.41$)	[75]
	Merkel cell carcinoma	JAVELIN Merkel 200 part B (phase II)	Single-arm avelumab	ORR 62.1%	[78]

Table 1 (continued)

Agents	Indication	Design/study	Regimen	Results	References
Combination					
	Melanoma	CHECKMATE-069 (phase II)	Ipilimumab/nivolumab vs ipilimumab	NR vs 4.4 months (HR 0.40; $p<0.001$)	[47]
	Renal cell carcinoma	CHECKMATE-214 (phase III)	Ipilimumab/nivolumab vs sunitinib	NR vs 26.0 (HR0.63; $p<0.001$)	[48]
IDO inhibitors	Melanoma	ECHO-202/KEYNOTE-037 (phase I/II)	Epacadostat + nivolumab	PFS 12.4 months; ORR 56%	[86]
		ECHO-301/KEYNOTE-252 (phase III)	Epacadostat + pembrolizumab vs placebo + pembrolizmab	PFS 4.7 vs 4.9 months (HR 1.0; $p=0.517$)	[87]
	Urothelial carcinoma	ECHO-202/KEYNOTE-037 (phase I/II)	Pembrolizumab + epacadostat	ORR 35%	[89]
	Renal cell carcinoma	Phase II	Indoximod + checkpoint inhibitor	ORR 55.7%	[90]

ORR objective response rate, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *NSCLC* non-small-cell lung carcinoma, *EORTC* European Organisation for Research and Treatment of Cancer, *SCCHN* squamous cell carcinoma of the head and neck, *HCC* hepatocellular carcinoma, *IDO* indoleamine 2,3-dioxygenase-1

Table 2 FDA approval of immunotherapy over the years

	2011	2014	2015	2016	2017	2018	2019
Ipilumumab	Melanoma		Stage III melanoma				
Nivolumab		Melanoma	mNSCLC mRCC	Hodgkin lymphoma mHNC mRCC	Stage III melanoma HCC MSI-h colon cancer Urothelial cancer	mSCLC	
Ipilimumab + nivolumabe			Melanoma			mRCC MSI-h mCRC	
Pembrolizumab		Melanoma	mNSCLC	mNSCLC first line mHNC	Hodgkin lymphoma mNSCLC first line plus chemotherapy Urothelial cancer MSI-h tumors Gastric cancer	Cervical cancer HCC Merkel cell carcinoma mNSCLC first line plus chemotherapy Mediastinal large B-cell lymphoma	mRCC plus axitinib Melanoma adjuvant
Atezolizumab				Bladder cancer mNSCLC		mNSCLC plus chemotherapy	mSCLC plus chemotherapy first line mTN breast cancer plus chemotherapy
Durvalumab					Urothelial cancer	Stage III NSCLC	
Avelumab					Merkel cell carcinoma Urothelial cancer		

mNSCLC metastatic non-small cell lung cancer, *mHNC* metastatic head and neck carcinoma, *mRCC* metastatic renal cell carcinoma, *MSI-h* microsatellite instability-high, *mCRC* metastatic colorectal cancer, *HCC* hepatocellular carcinoma, *mSCLC* metastatic small cell lung cancer, *mTN* metastatic triple negative

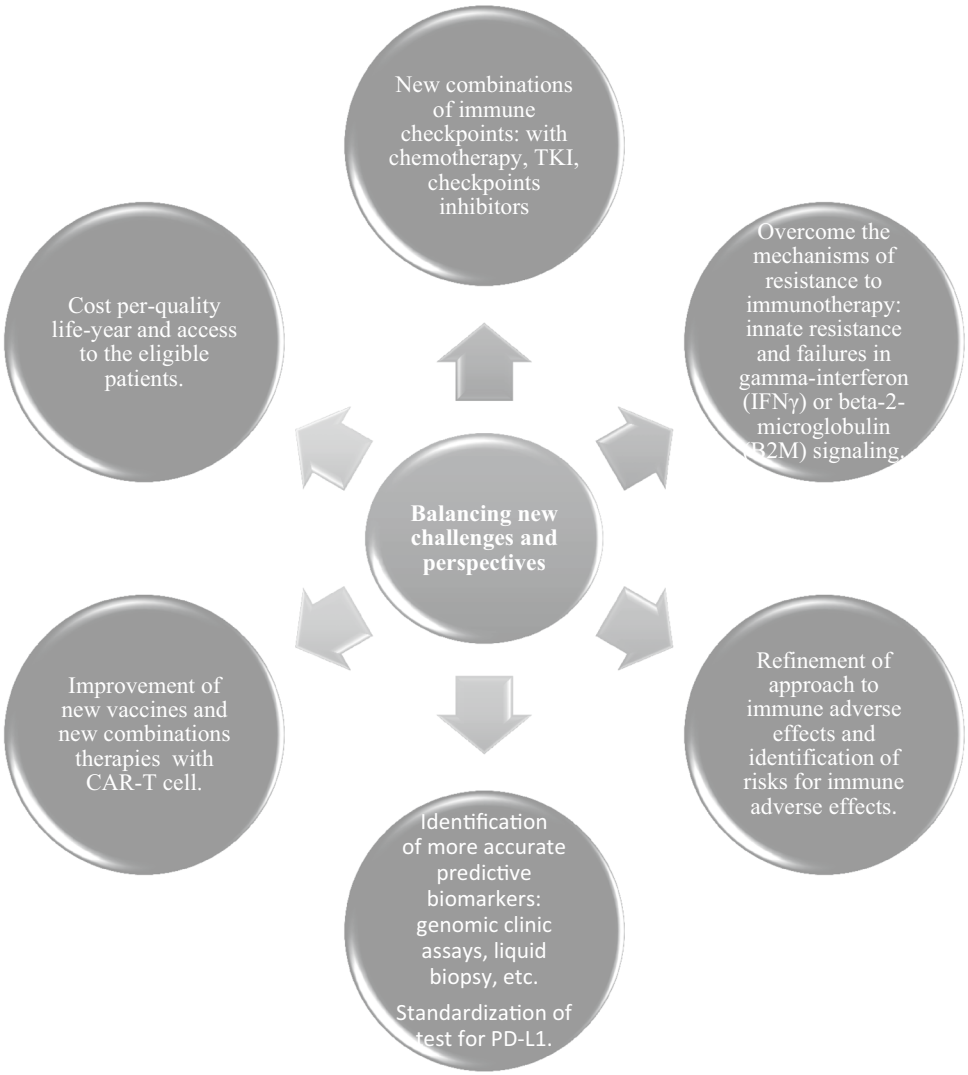

Fig. 1 Immuno-oncology: new challenges and future directions

Zacharakis et al. [13] reported a successful case of refractory breast cancer with complete durable regression using adoptive transfer of autologous lymphocytes reactive against mutant versions of four proteins-SLC3A2, KIAA0368, CADPS2 and CTSB. In a small clinical trial that recruited patients with metastatic cervical cancer for treatment with human papillomavirus-targeted tumor-infiltrating T cells, one third of patients had objective response [14].

Chromosomal replication can lead to telomere loss or shortening by 50–100 base pairs of DNA per cell division. This phenomenon has been described in T cells during the process of expansion and differentiation from naive to memory T cells that undergo extensive expansion, causing induction of cell death. However, this process is compensated by the action of telomerase, which has decreased activity with repeated antigen stimulation, leading to telomere shortening [15]. Telomere length of TILs correlates positively with clinical response to therapy as well as suggested as a marker of proliferative potential of the transferred T cell [16]. Similarly, CD27, expressed by naive and memory T cells but downregulated in late stage effector, has been assessed in studies of TILs therapy [17]. Higher numbers of infused CD8 + /CD27 + T cells are positively associated with clinical response to TILs, pointing to proliferative potential as a determinant of effective ACT in humans. However, these data are still inconsistent and there is considerable overlap in both telomere length and CD27 expression among responding and non-responding patients, which precludes the use of these markers to better select patients for ACT based on TILs [18].

Current efforts are focusing, not only on improving TILs therapy, but also on expanding other cell therapies for distinct malignancies. One of the ACT's strategies is to transfer genetically modified T cells expressing tumor-associated antigens (TAAs). Recently, the use of engineered T cells has taken place at the TIL extraction site since it is a more easily

performed procedure by enabling the acquisition of a highly specific T cell from the peripheral blood replacing the need for tumor extraction and expansion of TILs, regardless of the amount of lymphocyte infiltration into the tumor. The engineered T cells have a highly avid T cell receptors to the TAAs and may be modified for other costimulatory activities to improve clinical response. Mostly, they are chimeric antigen receptors (CARs), defined as single-chain antibodies, composed by variable fragments and linked to T cell receptor (TCR) and T cell costimulatory receptor signaling domains. These compounds connect with the cell-surface antigens in a non-major histocompatibility (MHC) restricted way, or even the traditional $\alpha\beta$ TCRs that recognize epitopes of intracelular antigens presented by MHC molecules [19–21]. Unfortunately, the results of studies with CAR T cells in solid tumors still remain disappointing [22].

Differently from haematological malignancies, the major challenge for the use of CAR T cell in solid tumors lies in finding a specific tumor antigen with no expression in normal tissues. Unacceptable rates of on-target, off-tumor toxicities in patients treated with CD19 and B cell maturation antigen (BCMA)-specific CARs, mainly severe haematological toxicities such as B cell and plasma cell aplasia, have been described in clinical studies [23]. The antigen density in tumor cells, coupled with activation and cytokine production, has been pointed out as a possible marker of CAR T cell functionality [24]. Since systemic administration has been shown to be harmful, another important challenge for CAR T cell use is to establish efficient trafficking to and expansion at the tumor site. One of the solutions can be by refining the chemotaxis of T cells to the tumor site and reginal delivery with a better understanding of the tumor microenvironment as an active agent [25].

Therapeutic vaccines

The therapeutic cancer vaccines do not have the limitation of benefiting a specific group of cancer patients because it has a less restrictive mechanism of action. As mentioned before, solid tumors are heterogeneous with regard to the expression of cell membrane antigens, which makes them more resistant to checkpoint blockade and ACT. The naive T cells are activated by antigen-presenting cells (APCs), such as dendritic cells, which are essential for the effective action of vaccines. Therefore, the active components of the therapeutic vaccines would be: formulations, delivery vehicles, tumor antigens and immune adjuvants [26]. On the other hand, minimal clinical effectiveness could be attributed to the poor pharmacokinetic properties resulting in rapid clearance.

Whole-cell vaccines are composed of autologous and allogeneic groups of modified tumor cells from the patient and non-self cells. The FDA approved an autologous vaccine composed of immune system cells for oncology use. Sipuleucel-T has shown reduction of 22% in the risk of death as compared with the placebo group (hazard ratio, HR 0.78, 95% CI 0.61–0.98, $p = 0.03$) [27]. Several allogenic cancer cell vaccines are being tested, including vaccines to treat several solid tumors of different sites [28]. However, none have proved effective enough to be licensed.

One of the main difficulties for the creation of effective personalized therapeutic cancer vaccines (peptide and genetic) is the identification of the most suitable antigens to use. Tumor neoantigens result from somatic mutations and are highly immunogenic. Although already identified as excellent antigenic targets, their identification was not possible until the recent availability of the next generation sequencing. Some research strands, such as The Cancer Genome Atlas (TCGA), based on RNA-sequencing data from thousands of samples across solid tumor, indicate that the number of neoantigens is directly proportional to expression gene activity signature of T cells [29]. The tumor antigen mRNA-transfected dendritic cell (DC) vaccines have been shown as the major focus of research involving DC vaccines, in which antigenic response is induced by T cells [30].

Therapeutic cancer vaccines as monotherapy have not shown consistent advantages. Despite appropriate antigen selection and vaccination platform, many agents failed due to lack of comprehension of immune-suppressive microenvironment and tumor cell-intrinsic mechanisms. Combinations of therapeutic vaccines with other immunotherapeutic agents have been shown to be synergistic and more effective. In a phase I/II study performed by Gibney et al. [31], a response rate (RR) of 30% and a median duration of response of 14.6 months were achieved in 92 ipilimumab-refractory patients with melanoma submitted to nivolumab and multipeptide vaccine.

Immune checkpoints

Immune checkpoint pathways operate at different levels of the immune response. Allowing the immune system to distinguish from self to non-self, these pathways generate an immune response to antigens although managing to prevent autoimmunity and maintaining a normal immunologic homeostasis. As previously said, the ability to evade the immune system is one of the hallmarks of cancer through specific inhibitory signaling pathways, such as the T lymphocyte-associated antigen 4 (CTLA-4), which is likely to occur peripherally in the lymph nodes by inhibiting T cell proliferation early in the immune response, and programmed cell death protein 1 pathway (PD-1/PD-L1), performing inhibitory processes in different sites of tumor [32, 33].

The CTLA-4 blockade conventionally modulates the early T cell response by a standard of regulatory feedback

inhibition. Naive T cell activation in the secondary lymphoid organs occurs simultaneously with costimulatory signals, such as the binding of the CD28 receptor from the T cell to the CD80 (also known as B7-1) and CD86 (or B7-2) from the APC. But, the CTLA-4 is also expressed on the surface of T cells and, thereafter, the inhibitory signal is bound by binding with B7-1 and B7-2 receptors, with higher affinity than the CD28. The main objective of the CTLA-4 pathway is to confer immune tolerance. PD-1, unlike CTLA-4, is an inhibitory regulator of effector T cell activity in peripheral tissues and tumor environment [34]. PD-1 interaction with PD-L1 (also known as B7-H1) and PD-L2 downregulates the antigen receptor signaling leading to immune cell activation [35]. PD-L1 is induced hematopoietic cells through the IFN-gamma produced by activated T and NK cells, whereas PD-L2 is more selectively expressed by dendritic cells and macrophages fundamentally induced by IL-4 [36]. Besides, not all circulating T cells do express the PD-1 receptor, being induced by T cell receptor (TCR) complex stimulation or exposure to cytokines such as IL-2, IL-7, IL-15, IL-21, and transforming growth factor (TGF)-β [37].

The immunologic checkpoint blockade with anti-CTLA-4 and anti-PD-1/PD-L1 antibodies have proven efficacy in several types of cancer. They activate T cells maintaining the proliferation and production of cytokines in the tumor microenvironment and, therefore, immune response to tumor antigens. However, immune-related adverse events (iRAEs) are likely to occur through nonspecific immunologic activation, including dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events. The treatment of these conditions usually involves temporary and careful immunosuppression with corticosteroid, which may negatively influence the efficacy of immunotherapy when used continuously and for long term, tumor necrosis factor α antagonists, mycophenolate mofetil or other agents [38].

Response evaluation criteria in solid tumors (RECIST) v 1.1, very efficient for cytotoxic chemotherapy, are not a reliable tool for use in the evaluation of response to immunotherapy [39]. In this setting, the immune-related response criteria (irRC), with better refinement, avoiding misleading tumor pseudoprogression, has become an option. By the new rules, new lesions are included in the total burden assessment without immediately being considered progressive disease (PD) and require confirmation of apparent initial disease progression on a subsequent radiographic assessment. The irRC was developed from experience with anti-CTLA-4 therapy trials, but some patients treated with PD-1 agents have similarly shown the same immune-related patterns of response. Some weaknesses noted are the higher interobserver variability, the time-consuming measurement and the fact that irRC was based on malignant melanoma specifically treated with anti-CTLA-4 or anti-PD-1/PD-L1 monoclonal antibodies (mAbs), which may differ from the effect of new drugs under development against different targets with different effect patterns [40, 41].

Anti-CTLA-4

Before immunotherapy, the standard treatment for patients with advanced melanoma was chemotherapy and median overall survival (OS) of patients was quite shorter, less than one year [42]. The CTLA-4 was the first checkpoint receptor to be clinically targeted. In an era lacking effective therapies in the treatment of melanoma, ipilimumab was firstly approved by FDA in 2010 for newly diagnosed or previously treated metastatic/unresectable melanoma based on a pivotal phase III study, reaching 10 months median OS with 46% survival rate at 1 year [43]. Thereafter, it was approved by FDA in 2015 for patients with stage III melanoma completely resected as adjuvant treatment based on the phase III study EORTC 18071, in which 40.8% were free of relapse ($p < 0.001$) and 65.4% were alive after a follow-up of 5.3 years ($p = 0.001$) [44]. Later on, PD-1 inhibitors (nivolumab or pembrolizumab) demonstrated survival gain and improved toxicity profile compared to ipilimumab, becoming the new first-line treatment standard for advanced melanoma [45, 46].

But, still in 2015, the combination of ipilimumab and nivolumab (anti-PD1 inhibitor) became the new standard treatment for newly diagnosed unresectable/metastatic melanoma without mutation of *BRAF*, approved by the FDA based on the phase II CHECKMATE-069, in which the new drug combination reduced the risk of progression or death by 60% compared with ipilimumab alone (HR 0.40, 95% CI 0.22–0.71, $p < 0.002$) [47]. Likewise, in April 2018, this same combination was approved as first-line treatment for intermediate or poor risk advanced renal cell carcinoma based on CHECKMATE-214, a randomized open-label phase III trial that reduced the risk of death by 37% over sunitinib (HR 0.63, $p < 0.001$) [48]. However, the already consolidated synergistic benefits of the combination ipilimumab and nivolumab, due to the chance of simultaneous inhibition of different immune checkpoints, are counterbalanced by the challenge of overcoming the higher immune-mediated toxicity rate as well as relative costs in use in lower–middle income economies.

As for the new CTLA-4 inhibitor, tremelimumab, Ribas et al. [49], through a large phase III study, failed to demonstrate statistically significant increase in survival over standard-of-care chemotherapy (HR 0.88, $p = 0.127$). The negative results were probably due to the selection of patients with a better prognostic profile and the fact that the patients in the comparator group were treated on the progression with ipilimumab, which was already widely available during the study. Tremelimumab as monotherapy or in combination was also tested for metastatic renal cell

carcinoma, metastatic colorectal cancer, and advanced gastric and esophageal adenocarcinoma; however, no clinically significant benefit was reported [50, 51].

Anti-PD-1

Nivolumab, a PD-1 inhibitor, was initially approved by the FDA in December 2014 for patients with non-mutated *BRAF* unresectable/metastatic melanoma refractory to ipilimumab. Right after, in March 2015, it was expanded for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. In the trial designed by Brahmer et al. [52], the risk of death was 41% lower with nivolumab than with docetaxel ($p < 0.001$). Thereafter, in 2017, nivolumab approval for use as adjuvant treatment for patients with node-positive completely resected melanoma was supported by the CHECKMATE-238, in which nivolumab reduced the risk of recurrence by 35% over the standard ipilimumab ($p < 0.0001$) [53].

As for other solid tumors, nivolumab is now a great option for treatment of advanced renal cell carcinoma, previously exposed to antiangiogenic therapy, based on a randomized trial that showed an increase of about 6 months in the median OS compared with the group control treated with everolimus ($p = 0.002$), regardless of PD-L1 expression [54]. Thereafter, some pivotal trials were driven toward the assessment of efficacy and safety of the use of nivolumab for head and neck cancer. In November 2016, the FDA granted nivolumab approval for patients with recurrent or metastatic platinum-resistant squamous cell carcinoma of the head and neck based on the positive results of the phase III CHECKMATE-141 trial, in which median OS was statistically significantly improved with nivolumab over single-agent chemotherapy (HR 0.70, 95% CI 0.53–0.92, $p = 0.0101$) [55].

For the context of platinum-refractory locally advanced or metastatic urothelial carcinoma setting, in May 2017, nivolumab confirmed its FDA approval for use through the CHECKMATE-275 trial, in which impressively 19.6% (95% CI 15.1–24.9) of patients responded to treatment with nivolumab, including 7 patients with complete response [56]. In the same year, FDA approved nivolumab for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan supported by the results of CHECKMATE-142 trial that reported 31.1% (95% CI 20.8–42.9) of ORR [57]. In June 2017, nivolumab also emerged as a new option for patients with sorafenib-resistant hepatocellular carcinoma, based on the results of phase I/II CHECKMATE-040 trial that showed 20% (95% CI 15–26) of ORR in the dose-expansion phase [58].

As for the anti-PD-1 agent pembrolizumab, the first FDA approval was for use in patients with advanced unresectable recurrent melanoma based on the positive results of KEYNOTE-006 trial, which showed a 32% reduction in the long-term risk of death over the control group with ipilimumab ($p = 0.0009$) [59]. Subsequently, the use of pembrolizumab as monotherapy in patients with previously untreated advanced NSCLC with PD-L1 expression greater than 50% of tumor cells was supported by the impressive results of two phase III trials, prolonging the median OS in more than 15 months over the use of cisplatin-based chemotherapy [60] and decreasing the risk of death by 31% [61]. With some preclinical evidence that chemotherapy modifies favorably the immunogenic tumor status, the combination of pembrolizumab with platinum-based chemotherapy for NSCLC without sensitizing *EGFR* or *ALK* mutations as first-line treatment has become a standard, regardless of PD-L1 status, virtually doubling the ORR in an early clinical trial [62]. These positive results were recently confirmed by large published phase III studies for nonsquamous NSCLC [63] and squamous cell NSCLC [64].

Further indications of pembrolizumab for other solid tumors have been based on the results from pivotal clinical trials with promising results, some cases with traditionally "hard-to-treat" tumors. KEYNOTE-012, which showed responses of 6 months or longer observed in 82% ($n = 23/28$) of the responding patients [65]. As for the first-line setting in cisplatin-ineligible advanced urothelial cancer with PD-L1-expression cutoff of 10%, a single-arm phase II trial presented 38% of ORR (95% CI 29–48) [66]. The results of KEYNOTE-158, the multi-cohort trial, led to the approval of pembrolizumab for use in patients with recurrent or metastatic cervical cancer expressing PD-L1 platinum refractory, in which ORR was 14.3% (95% CI 7.4–24.1) and the median duration of response for responders has not yet been reached (95% CI 4.1–18.6+) [67]. Other tumor sites, such as PD-L1 positive recurrent metastatic gastric or gastroesophageal junction adenocarcinoma [68], and MSI-H solid tumors refractory to standard cytotoxic treatments without consolidated treatment options [69, 70], were also approved for the use of pembrolizumab as monotherapy.

Anti-PD-L1

Atezolizumab, an IgG1 antagonist antibody to PD-L1, was approved by the FDA for the treatment of metastatic NSCLC with progressive disease after platinum-based chemotherapy and/or anti-EGFR/ALK therapy. In the phase III OAK trial, patients with recurrent advanced NSCLC, regardless of *EGFR/ALK* mutation and PD-L1 status, had an increase in median OS in more than 4 months ($p < 0.001$) [71]. In the IMpower 150 trial, PD-L1 unselected advanced nonsquamous NSCLC had an improvement in the risk of death

by 22% when exposed to the combination of atezolizumab with chemotherapy alone ($p = 0.016$). This benefit was also surprisingly observed in patients with *EGFR* and *ALK* mutation [72].

Atezolizumab is additionally indicated for the treatment of recurrent platinum-refractory advanced urothelial carcinoma, based on the results of clinical trials that demonstrated durable activity and good toxicity profile in this population [73–75]. The use as first-line therapy for patients with cisplatin-ineligible advanced or metastatic urothelial carcinoma was based on a single-arm phase II trial, in which the ORR was 23% (95% CI 16–31) and the CR rate was 9% ($n = 11$), and 19 of 27 responses were ongoing at 17.2 months' median follow-up [76]. For other tumor types such as breast cancer, renal carcinoma, mesothelioma, melanoma, and other malignancies, clinical trials with atezolizumab, combined with chemotherapy/monotherapy, are still ongoing and will provide more information about immunotherapy benefits in these settings.

In May 2017, FDA granted conditional approval for avelumab, another anti-PD-L1 agent, for the treatment of advanced urothelial carcinoma, based on the results of the combined analysis of two phase I expansion cohorts that showed an ORR of 17% (95% CI 11–24), including 6% of CR, presenting a more unfavorable toxicity profile compared to other checkpoint inhibitors [77]. Another prospective clinical study with some cohorts of patients with different settings of advanced urothelial cancer demonstrated ORR ranging from 33 to 62.1% [78]. More data on the use of avelumab are currently being evaluated in ongoing clinical trials for different indications, as for renal carcinoma in association with axitinib, for solid tumors in association with chemotherapy or immunotherapy, for head and neck cancer [79–82].

Durvalumab, a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 (B7.1), was approved in May 2017 for metastatic urothelial carcinoma after platinum-based chemotherapy, based on a phase I/II, in which durvalumab demonstrated favorable clinical activity with 17.8% ORR (CI 12.7–24.0%), including 7 complete responses, with a manageable safety profile [83]. Durvalumab was approved in February 2018 for patients with stage III unresectable NSCLC whose disease has not progressed following platinum-based chemoradiotherapy. In the phase III PACIFIC trial, consolidation with durvalumab dramatically increased PFS in more than 10 months over placebo ($p < 0.001$) [84].

IDO inhibitors

Indoleamine 2,3 dioxygenase (IDO) is an enzyme that catabolizes the first and rate-limiting step in the degradation of the essential amino acid tryptophan to kynurenine. The tryptophan depletion and production of kynurenine and other catabolites limit antigen-dependent T cell activation, resulting in immune tolerance to antigens in tissue microenvironments. In the normal physiologic state, IDO is important to create an environment that limits damage to tissues due to an overactive immune system. But on the other hand, it can facilitate the survival and growth of tumor cells expressing unique antigens that would be recognized by immune system. IDO expression has been correlated with decreased OS and PFS in several clinical studies [85].

An increasing number of trials including IDO inhibitors are still ongoing, but some data already published present controversial results. The combination of pembrolizumab plus epacadostat, an inhibitor of IDO1, has been evaluated in phase I/II study ECHO-202/KEYNOTE-037 for advanced tumors. The data of the melanoma cohort, in treatment-naive patients, have shown attractive results, in which ORR was 56% (25/45; 6 CR, 19 PR), regardless of PD-L1 and *BRAF* mutation status, with just 17.2% of patients experiencing grade 3 or greater immune-related adverse events [86]. Nonetheless, the data from a phase III ECHO-301/KEYNOTE-252 showed that epacadostat plus pembrolizumab in this setting did not result in significantly longer PFS versus placebo plus pembrolizumab (median PFS 4.7 versus 4.9 months, HR 1.00; 95% CI 0.83–1.21; $p = 0.517$). And findings were consistent across PD-L1 and *BRAF* subgroups [87]. Likewise, the initial data from phase II ECHO-204 study with the combination epacadostat plus nivolumab for advanced melanoma showed promising antitumor activity, with 62% of ORR (9 CRs, 22 PRs). Unfortunately, the regimen was very toxic, with 48% of the patients presented grade 3 or more toxicity [88].

As for other non-melanoma cancers, ECHO-202/KEYNOTE-037 evaluated some cohorts of solid tumors from other sites. In the platinum-refractory urothelial carcinoma cohort, the combination of pembrolizumab and epacadostat showed ORR of 35% (13/37; all PR). In the renal cell carcinoma cohort, 33 patients were evaluated, 64% were MSKCC intermediate risk, reaching an impressive 47% of ORR (9/19; 1 CR, 8 PR) and, at the date cutoff, 100% of responders were still ongoing. Grade 3 or 4 adverse events occurred in only 15% of the patients [89].

Indoximob, another IDO inhibitor, was evaluated in a phase II trial in association with investigator choice checkpoint inhibitor for patients with heavy-treated advanced

melanoma. The results showed great benefit among patients treated with pembrolizumab and indoximob; ORR was 55.7% (39/70) and CR was 18.6% (13/70), having been well tolerated with easily manageable side effects [90]. As a promising drug in the field of immunotherapy, with interesting preliminary results, many studies are ongoing assessing its efficacy and safety in different settings of solid tumors as monotherapy or in combined regimens.

Conclusion

Systemic therapy for a long time has been mastered by cytotoxic chemotherapy. But recently, the concept of immunotherapy as a modulator of the patient's immune system to battle neoplastic cells became an important weapon against cancer. Immune checkpoint blockade has certainly been one of the most imposing developments made in cancer in recent decades. Immuno-oncology has become a field under rapid and exuberant evolution, with many agents being developed and studied for their potential to improve long-term survival of several tumor types in different settings with considerable success. Throughout this review, many important data regarding the new treatment proposals have been presented.

Predicting clinical efficacy to immune checkpoint blockade remains as a major challenge. The lower response rate to the agents in some settings and the higher cost of drugs with a significant economic impact on the health care systems demand a careful personalized approach. Searching for reliable predictive biomarkers, several strands have focused on tumor immune phenotype, somatic genomic features, or the gut microbiome.

Several studies in different tumor types have shown that patients whose tumors express PD-L1, detected by immunohistochemical assays, have higher response rates to PD-1/PD-L1 blockade than patients who do not express PD-L1. Despite this, specific groups of patients who do not express PD-L1 can still have some degree of response to PD-1/PD-L1 blockade, demonstrating that other biomarkers are still needed to provide better prediction of patients who benefit from the immunotherapeutic treatment [91].

Solid tumors with high number of non-synonymous genomic mutations (MSI-H) have increased T cell infiltration and higher responses to immune checkpoint blockade. TCGA data have demonstrated that mutations in *JAK1* were associated with high mutation burden and microsatellite instability occurring in multiple tumor types including endometrial, colorectal, stomach and prostate carcinomas and may play a role in immune evasion and evasion to checkpoint inhibitors [92].

Immunological genetic signatures were evaluated in a large study that enrolled 1535 patients with advanced solid tumors treated with immune checkpoint inhibitors. In this trial, the leukocyte antigen class I (HLA-I) genes were factors that significantly influenced survival in patients with melanoma and NSCLC. For instance, the HLA-B44 profile was associated with prolonged OS, whereas the HLA-I homozygosity and loss of heterozygosity (LOH) represented a genetic barrier to effective immunotherapy response [93].

As a future biomarker, the intestinal microbiota is likely to play a role in the development of cancer as a prior toxin secretion and DNA damage, dysbiosis and inflammation with increased pro-inflammatory signals, inducing immunosuppression and tumor evasion. With the development of immunotherapy, it has been proven that the composition of the gut microbiota has also an impact on the response to the anti-PD-1/PD-L1 agents in patients with epithelial tumors or melanoma [94]. These results were suggested in a prospective study, in which tumor biopsies, oral and gut microbiome and blood samples were collected from 112 patients with metastatic melanoma treated with anti-PD1 agents at specific times throughout the treatment to explore genomic alterations, as well as density of tumor-infiltrating lymphocytes. Metagenomic analysis revealed a functional difference in gut bacteria between responders and non-responders. Analysis of patient fecal microbiome samples showed significantly higher alpha diversity ($p < 0.01$) and relative abundance of the Ruminococcaceae family ($p < 0.01$) among responders [95].

Through simultaneous anti-cancer activities on different fronts, involving different mechanisms of action with synergic effect, these new strategies offer the opportunity to defeat the many barriers that protect tumor cells from the innate and adaptive immune system. Therefore, combining immunotherapy with different therapies may improve survival in a greater number of patients when compared with monotherapy. Establishing strategies in how to make progress in this field and how to apply these new therapies most effectively to achieve the best outcomes is crucial. So far, the great challenge is to select the best combined treatment for each setting and overcome the higher limiting dose toxicities that occur in some cases. Finally, balancing risk and cost-saving schemes are completely imperative.

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